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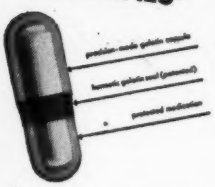

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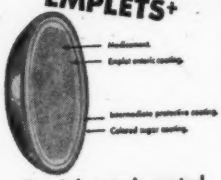

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EDITORIAL

"PEACE ON EARTH, GOOD WILL TOWARD MEN"

THERE is no better time than the Christmas season for a careful analysis by both men and nations, who call themselves Christian, as to whether their thoughts and deeds are in accordance with the teachings of Christ.

An outside observer, if such were possible, would find little in the current world chaos to substantiate the commonly accepted belief that Christian brotherhood now or has ever controlled the affairs of men, even in the so-called Christian nations. But, after all, Christianity is not a pattern in conformity with which each Christian must fit, but rather an ideal toward which each must strive, with full realization that it cannot be totally achieved.

War has ever been a calamity to those who are devout in their beliefs, and the Church has sought many means to rationalize Christian principles with the pursuit of war. To many these reasons seem valid, but to others there can be no satisfactory argument justifying war for any cause.

A recent statement, however, made by one of our leaders urged the American people to learn to hate! This was most unfortunate, both in so far as the expression itself was concerned and in the calamity which will surely result, if this advice is followed. The progress of offensive warfare might conceivably be improved if personal hatred of our enemies were added to the many reasons we already have for fighting them. But victory over our enemies is only a means to an end—*peace on earth.* This end envisions a peace in which a true family of nations will be maintained with justice and honor for all and with no restrictions laid down by race, color, or creed. Even now some of our great leaders, who fully grasp the meaning of this, are developing a blue-print for just such a peace.

Hatred is a disease which slowly but surely warps men's souls. If we are to be poisoned by it for the mental and physical stimulus it

offers, then like the cocaine-addict we shall become incapable of a return to normalcy, and all hope for a just and lasting peace ends. If, with victory achieved, the American people are not mentally conditioned to both accept and demand a just peace, then we shall lose the peace just as we did following the last war, and still another generation will be required to pay the terrible cost of such error.

That we shall win this war decisively there can be no doubt, and it is not disloyalty which leads us to challenge the need for hatred. We can successfully prosecute our fight against evil without hating the enemy peoples. Let us be mindful of our Lord's admonition so frequently quoted and revered, "For what shall it profit a man if he shall gain the whole world and lose his own soul?"

The real danger, indeed, is in the growth of hatred which may be expected to develop with mounting casualties, privations and hardships. If America succumbs to these influences, then the hope and future of countless millions the world over is destroyed, and America will lose forever her God-given chance to restore decency and respect to all mankind.

L. F. Tice.

MODERN ANTIMALARIALS *[1]

By Maximilian Ehrenstein, Ph. D.

Assistant Professor of Chemistry Assigned to Medicine,
School of Medicine, University of Pennsylvania

FROM the viewpoint of prevalence, malaria appears to be the most important disease in the world today. It is a very ancient disease and has been a determining factor in the progress of civilization. Its ravages have decimated entire populations. History shows that malaria has checkmated invading armies and balked attempts at empire building. It is certain that it will also play its part in the present war. It may well be that it will affect or even decide entire campaigns. Reports say that Bataan finally fell into the hands of the Japanese partly because, due to a lack of quinine, the defenders were exhausted from malaria. Recent news from India stated that the British armies which are stationed at the Burmese-Indian frontier have just recuperated from the very ill effects of malaria.

This plague was formerly supposed to be due to poisonous emanations from damp ground. Hence the Italians called it "mala aria", contracted to "malaria", which means "bad air". This term appears in practically all languages. The various types of malaria were known to Hippocrates, who mentions them in his book on epidemics. As far as the character and the transmission of the disease are concerned, mankind remained in the dark until about sixty years ago. Fortunately a valuable remedy, cinchona bark, was found centuries before the true character of malaria was recognized.

In most textbooks one finds the story that in 1638 the wife of the Count of Chinchon, the Viceroy to Peru, was stricken with malaria in the city of Lima. No cure was forthcoming until the Spanish governor of the neighboring town of Loxa produced a powder from bark which, to the amazement of all, caused her immediate recovery. On her return to Spain the Countess is said to have entrusted large

*Lecture delivered before the Philadelphia Branch of the American Pharmaceutical Association on November 10, 1942.

[1] The literature used in preparing this lecture is listed in the bibliography. Reference is made to it only in special instances because a great deal of this material is of a rather general character. The discussion of the malaria parasites is drawn largely from the chapter on Malaria in Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases (1).

quantities of the bark to her physician, Dr. Juan de Vega, who cured many persons on the Chinchon estates in Southern Spain. The story tells that by 1640 the use of the drug had spread over Europe. Linné, who named the genus of quinine-producing trees about 100 years later, left out the first "h" in the name Chinchon, hence there originated the mistaken spelling Cinchona. This romantic story has been undermined by the recently unearthed diary of the Count of Chinchon which gives what appears to be the more correct history of the discovery of the antimalarial action of cinchona (16). At the end of the sixteenth and beginning of the seventeenth centuries there was a considerable export of medical substances from the New World to Spain and Italy. Among the products exported was the bark of a tree which from the descriptions given was that of *Myroxylon peruiferum.* From this bark was obtained Peruvian balsam, used early in the seventeenth century as a febrifuge. Unfortunately for the exporters of medicinal substances from South America to Europe the supply of the bark from *Myroxylon peruiferum* was not sufficient to meet the demand, so the exporters resorted to the adulteration of Peruvian bark by another similar one. This bark, which gradually replaced the other, was undoubtedly derived from cinchona trees. The report (16) on this historical investigation closes with the following cynical statement: "It is a curious reflection that we thus owe one of our most successful chemotherapeutic remedies not to man's scientific acumen and research but to his dishonesty and greed."

The year 1880 was an important one in the history of malaria. In that year the French army surgeon Laveran in Algiers first demonstrated the living organism in the blood of a patient. After further investigations by other workers Ross and Grassi, in 1898, demonstrated the mosquito transmission of malaria.

Before entering into a discusion of the various antimalarials a description of the malarial infection and of its transmission should be given. The organisms which are responsible for malaria in humans are transmitted by certain Anopheles mosquitoes. So far 1400 different species of mosquitoes (*Culicinae*) have been accounted for and of these approximately 180 belong to the genus *Anopheles.* Only about 60 of these Anopheles species have been incriminated in the transmission of malaria, be it by natural or experimental infection. However, relatively few are of practical importance. While in the United States and Europe only 2 or 3 species are of primary signifi-

cance, a total of 13 species are under suspicion in India, which is known to be heavily infested with malaria. As can be imagined, the study of these transmitters or vectors of the malaria organisms is a specialized field of entomology. Its knowledge is necessary for the taking of effective sanitary measures against malaria. For our present topic it is of minor importance.

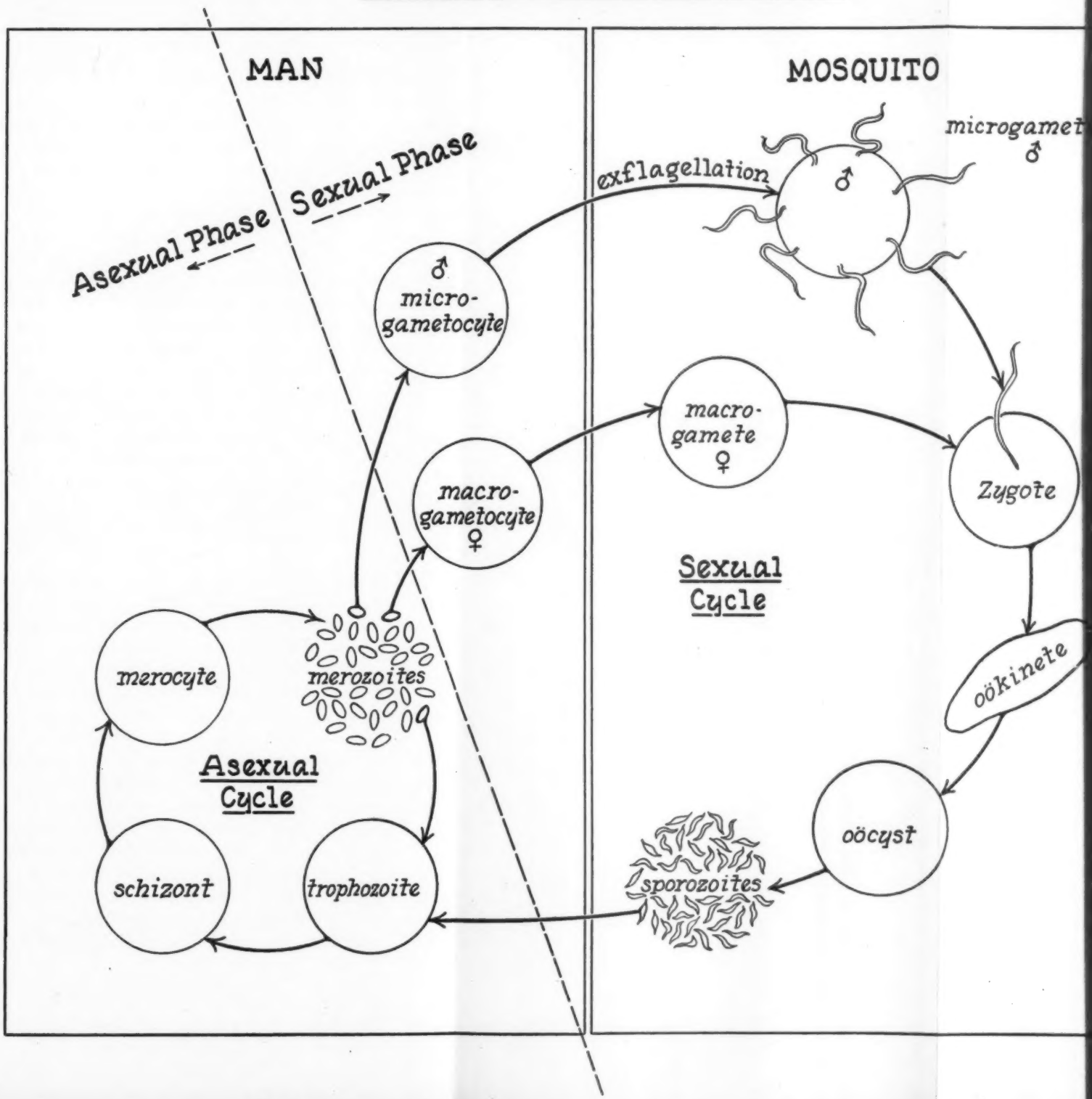
The organisms which produce the various types of malaria are parasites, which implies that they feed on a host. Unlike bacteria, they are classified as animals; they belong to the phylum *Protozoa,* to the class *Sporozoa* and to the genus *Plasmodium.*

All of the parasites belonging to the genus Plasmodium have a sexual and an asexual cycle of development. The sexual cycle takes place in the mosquito, which is considered the host for these parasites. The asexual cycle is passed in man, who is considered the intermediary host. In order to perpetuate its existence the parasite has to alternate between these two hosts.

When a mosquito feeds on a human being, the malaria parasites, which in this stage of development are called sporozoites, are transmitted into the blood stream.[2] After an interval, the history of which is still in doubt, the parasites enter the red blood cells where they begin to grow. During this phase of growth in the erythrocytes they are called trophozoites. In the full grown trophozoite nuclear division takes place. From this stage on the organism is called schizont from the Greek "schizontos" which means "cleaving" or "splitting". There are several subsequent nuclear divisions. With the nuclear divisions completed, the schizont reaches its mature form; it is now called a merocyte. The merocyte fills the greater part of the former red blood cell. Rupture now takes place liberating into the blood plasma from 8 to 32 spore-like bodies called merozoites. Besides the merozoites, toxic substances are liberated into the blood stream; they stem from the disintegrated red cells. The merozoites seek out and penetrate fresh red blood cells. There they develop into trophozoites, and the cycle is repeated. Multiplication by nuclear division or schizogony goes on in geometrical progression for about two weeks. This is called the incubation period. By then a sufficient number of parasites has been produced to cause clinical symptoms. It is estimated that there must be about one billion in the entire human body. There is usually a tendency for the parasites to develop

[2] See diagram.

Life Cycle of Malaria Parasites



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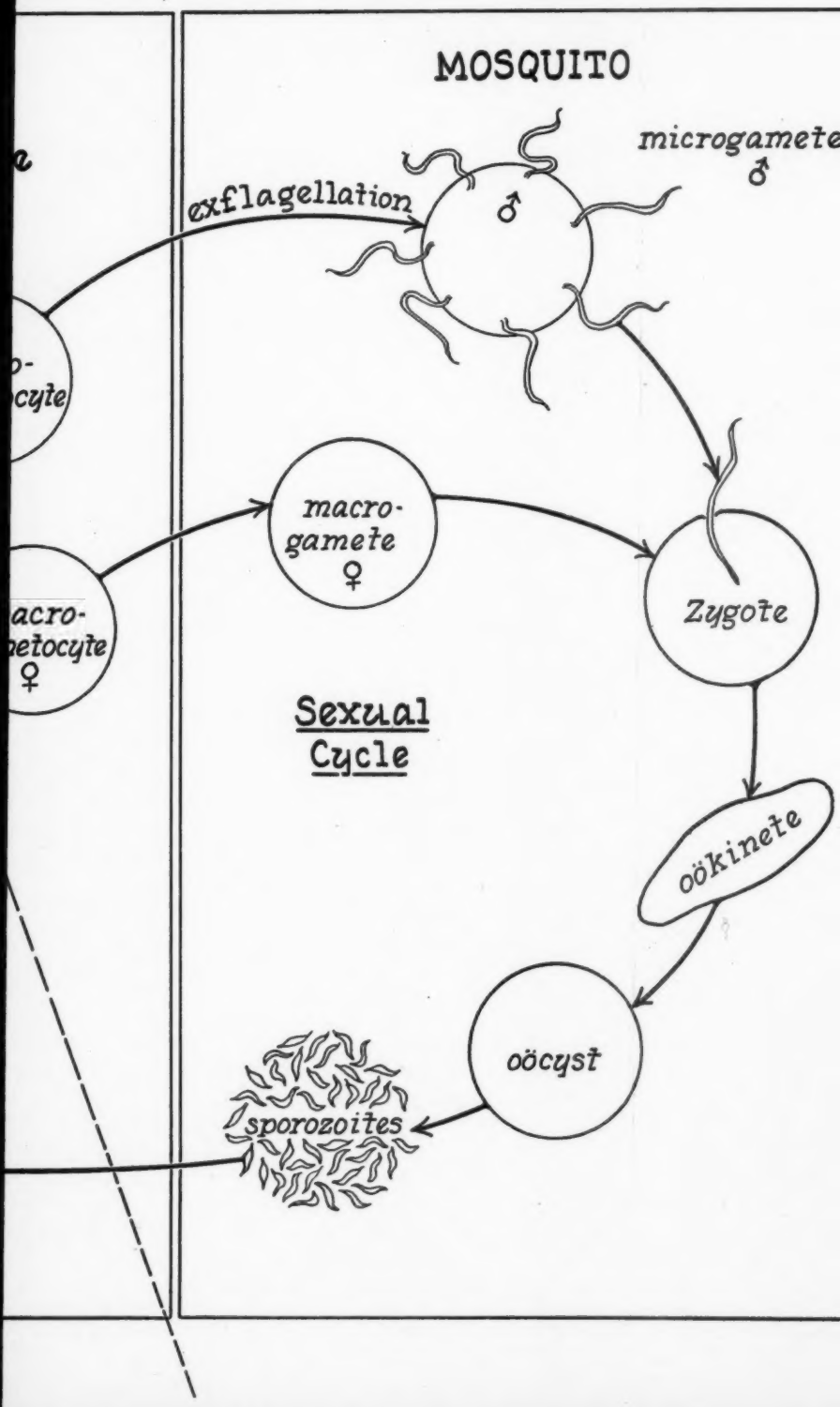


at nearly the same rate and to fall gradually in one or more groups, all members of which show about the same stage of development. Sporulation, i. e. liberation of the merozoites, occurs at about the same time within each group. The sporulation coincides with the onset of the malarial paroxysm. The malarial attack is attributed to the sudden liberation into the blood of toxic material originating from the disintegrated red cells. Since the merozoites develop by way of growth and subsequent division from a single, original cell, this is an asexual cycle.

Sexual forms of the malaria parasites appear in the peripheral blood at varying intervals after the attacks have become manifest. The sexual forms are called gametocytes. As will be seen they develop into gametes, which are the real sex cells. The manner of change from merozoites to gametocytes is rather obscure. It is virtually impossible to distinguish a young stage of a gametocyte from the asexual form. A number of malariologists are of the opinion that the repeated fever attacks change the conditions of the blood in such a way that it is no more an optimal medium for the development of the asexual forms. Consequently the formation of merozoites becomes reduced and, besides, some of them develop into gametocytes. Whether the suppression of the formation of merozoites can be interpreted in terms of an immunity is doubtful.

The gametocytes complete their growth in a period which is about double that of the schizonts. We differentiate between microgametocytes which are the male forms, and macrogametocytes which are the female forms. When blood containing gametocytes is taken into the stomach of a suitable Anopheles mosquito, the female gametocyte undergoes a certain change which causes it to become mature; it is now called a female gamete or a macrogamete. The male gametocyte, on the other hand, undergoes a process which consists of the extrusion of long and slender, whip or thread-like organisms. This process, which is called exflagellation, furnishes from 4 to 8 of these organisms. These flagella, which are highly motile, represent the mature male gametes; they are called microgametes. These microgametes move about in the stomach of the mosquito until they find a macrogamete. Such a macrogamete is now penetrated by a single microgamete. As is known, the union of two sex cells is called fertilization and the product of fertilization is a zygote. The zygote, which first has a rounded shape, later becomes elongated and motile. This

form, which is termed oökinete is capable of wormlike movements. It eventually penetrates the wall of the stomach and develops into a so-called cyst. This oöcyst represents a round wart-like protuberance on the outer surface of the stomach wall. The contents of the oöcyst now undergo important changes. There are several successive nuclear divisions and finally the oöcyst appears filled with sporozoites. There may be several hundred to 10,000 sporozoites in a single cyst, and there may be 500 cysts in the stomach of a single mosquito. As far as is known the mosquito suffers no ill effects from this symbiosis. When the development within the oöcyst is completed, rupture takes place and the spindle shaped sporozoites are released into the body cavity of the mosquito. Many of them migrate into the salivary glands. When a mosquito feeds on a human being, they are apt to be transmitted into the blood stream, where, as was stated before, they will initiate an asexual cycle.

There are mainly three species of the genus *Plasmodium* [2a] which cause attacks of malaria. *Plasmodium vivax* causes benign tertian malaria. The attacks come in 48 hour intervals. If the occurrence of one paroxysm is counted as the first day, the next one will happen on the third day. For the latter reason this type of fever is called tertian malaria.

Plasmodium malariae is responsible for the transmission of quartan malaria, the attacks of which occur every 72 hours. If one attack is counted as the first day, the next one will come on the fourth day. Hence one speaks of quartan malaria.

Plasmodium falciparum produces so-called malignant tertian malaria. Synonymous are tropical malaria or estivo-autumnal malaria. As in the case of the benign form the attacks occur every 48 hours.

The various forms of malaria are recognized from their clinical symptoms. Because in acute cases the parasites appear in the peripheral blood, so-called blood smears are taken as a further check. The microscopic examination of these smears permits one to distinguish clearly between the several species of Plasmodium. The intervals between the attacks of all three types of malaria usually correspond to one whole life cycle of the asexual forms of the parasites. Hence the cycle of schizogony requires 48 hours in tertian malaria and 72

[2a] A discussion of the more recently discovered *Plasmodium ovale* is omitted.

hours in quartan malaria. It is known that there are various strains or races within the same species of Plasmodium. This may cause differences of virulence. As indicated before, it can also happen that the parasites go through their cycles in two groups. Even though this does not change the length of each cycle, such a behavior will cut the time between two malaria attacks approximately in half. Such cases have been observed with all types of malaria parasites and they are especially known in connection with *Plasmodium falciparum* which causes tropical malaria. In this latter case the name *Plasmodium falciparum quotidianum* is applied. The adjective *"quotidianum"* implies that the attacks occur daily.

In the benign tertian and quartan infections an attack begins usually with a characteristic chill which radiates from the spinal column to the extremities and the jaws. This causes the teeth to chatter and the whole body to shake. The chill or rigor occurs when the merocytes rupture. Thereby the merozoites and toxic disintegration products of the red blood cells are released into the blood stream. This cold stage lasts for 20 to 60 minutes. It is followed by a hot stage, lasting from one to four hours, during which the patient runs a high temperature (105-106° F.). This is succeeded by a phase of profuse sweating, which is also called the period of defervescence. Thereafter the patient usually falls asleep and later awakens somewhat weakened but with a feeling of well-being. He now has a respite until the onset of the next attack. In the case of malignant tertian malaria the phases of the clinical manifestations are not as clear-cut as in the benign forms. They will not be discussed. It may be mentioned that the simultaneous infection by several species of malaria parasites is possible. In such an event the clinical picture deviates from that outlined above.

As was pointed out, the cycles of the asexual parasites bring about a wholesale destruction of red blood cells. Not only are the infected cells destroyed, but due to the liberated toxins non-infected cells suffer hemolysis. Hemolysis is the dissolution of the red cells which brings about liberation of the hemoglobin. As can easily be imagined, this condition leads to anemia. The degree of anemia depends on the type as well as on the length of the infection. It may be very severe. In malignant tropical infections the hemolysis may become so pronounced that hemoglobin appears in the urine (hemoglobinuria). In such a case one speaks of blackwater fever.

When a person becomes infected either with benign tertian or with quartan parasites, the defensive mechanisms of the individual soon come into action and, after a certain period, the parasites disappear from the peripheral blood stream. They tend to become localized mainly in three organs, namely the liver, the spleen and the bone marrow. Under these conditions, the spleen appears frequently enlarged, a symptom which is termed splenomegaly. In some instances, however, the parasites also continue to multiply in the peripheral blood. This applies especially to the tropical form of malaria. Even though in these cases localization in the mentioned organs takes place, this fails to counterbalance the unrestricted reproduction of the parasites. If it remains unchecked, the infection may ultimately become overwhelming and lethal.

In case the parasites disappear from the peripheral blood and become localized in certain organs, the infection slips into a latent stage during which an individual is free from attacks and may also be immune against a fresh infection. This does not mean that an immunity in the strict sense has been acquired. When such an individual is exposed to great fatigue, or hardship, or cold, the resistance may become temporarily lost and a malarial paroxysm may be precipitated.

Malaria is not only widely distributed over all parts of the tropical and subtropical world, but also over several of the more temperate regions. The northern and southern limits follow, although not precisely, the mean summer isothermal lines of 60° F. (60° N. to 40° S. latitude). *Plasmodium malariae* which causes quartan malaria has generally a very limited distribution. Of practical importance are mainly *Plasmodium vivax* and *Plasmodium falciparum* which are responsible for benign and malignant malaria respectively. The benign form is more prevalent in the temperate zones whereas the malignant form is predominant in the subtropical and especially in the tropical regions. The infested territories represent more or less ideal breeding places for the Anopheles mosquitoes. The climate must be moist and warm. Generally, malaria is more prevalent in rural districts than in cities. This is due to the fact that the former, i. e. the rural districts, offer better breeding places for the mosquitoes.

In the United States the disease is of practical importance in certain Southern and Southeastern States. The lethal cases are mainly due to the malignant tertian malaria. Due to effective control

measures the disease does not reach dangerous proportions in this country, in spite of the fact that the number of infections is estimated to average four million.

Except in certain regions around the Mediterranean and a few scattered cases elsewhere the disease is practically non-existent in Europe. It is widely distributed in most tropical and sub-tropical regions of the world. Doubtless a great number of these districts are already or will become scenes of military operations. Mortality from malaria is especially high in India, in most parts of Africa (especially Central and West Africa), and in certain parts of South America, especially Brazil. In the Pacific Islands, e. g., the Philippines, there are many cases of malaria. The Solomon Islands are badly infested, so are the New Hebrides, as are many Pacific territories which may become theatres of war. Certain islands, however, in the Pacific are free from malaria due to the fact that they do not harbor any Anopheles mosquitoes. The Hawaiian Islands, the main American bulwark in the Pacific, are free from malaria; so are the Fiji Islands, Samoa and Tahiti. Of islands at present occupied by the Japanese, the Ellice Islands and Gilbert Islands are free from malaria. There is always a possibility, however, that mosquitoes will be carried into non-malarious regions by way of fast moving vehicles, such as airplanes. Experts fear that malaria may be introduced to the Hawaiian Islands before the end of this war (13).

Effective measures against malaria may be divided into two groups:

1. General and prophylactic measures to prevent infection.

2. Therapeutic measures after infection has taken place.

General control measures deal in the first case with the Anopheles mosquitoes. Depending on the circumstances they may consist of:

a. The avoiding, if possible, of areas in which Anophelines are endemic.

b. The elimination of mosquitoes and their larvae by means of insecticides or other agents.

c. The elimination of breeding places for mosquitoes by way of systematic draining.

d. The protection from mosquito bites by screening, the use of bed nets, protective clothing and, in some instances, the use of so-called insect repellents.

Such general control measures have certainly gone a long way in preventing infection. The incidence of malaria among American soldiers in the Panama Canal Zone (about 78% of cases are due to *Plasmodium falciparum*) has been kept at a comparatively low level partly due to such measures.

As can easily be understood, general control measures cannot be well carried out during mobile warfare, when the armed forces have to move through malarious regions. The question arises whether under these circumstances, efficient chemoprophylactic steps can be taken to prevent infection or, at least, prevent acute malarial attacks.

The remainder of this lecture will be devoted to a discussion of agents which may be useful either as chemoprophylactics or as chemotherapeutics in the treatment of malaria. The aim of chemotherapeutic action is to eliminate:

1. The sporozoites which are injected into the blood stream by mosquitoes. Such an effect would be real chemoprophylaxis.

2. The asexual forms of the malaria parasites which are responsible for the clinical picture.

3. The sexual forms, i. e. the gametocytes in the blood of patients. As far as the individual is concerned, it makes no difference whether he carries sexual forms in his blood or not. They do not multiply in the human host and hence they do not cause any symptoms. Such an individual is, however, a malaria carrier who may pass on the sexual forms to a mosquito which in turn will infect other humans.

From the view point of the available drugs, the asexual forms are easiest to cope with, whereas the gametocytes and particularly the sporozoites are rather resistant.

Before reviewing the individual drugs it is advisable to mention the methods which may be used for the testing of new chemical substances before they are tried out in cases of human malaria.

Attempts have been made to test antimalarial compounds in vitro. For this purpose the respiration of certain species of Plasmodium may be measured in a Warburg apparatus. The addition of

certain drugs, some of them known to possess antimalarial action, will inhibit the respiration. No clear interrelationship between this action in vitro and therapeutic efficiency in vivo has been established. The method so far has been only of limited value.

Among animals, monkeys have been used for testing only to a minor extent. There are several birds which are suitable test animals, among them especially canaries. In Roehl's test the birds are inoculated with certain parasites which are related to the species causing human malaria (e. g. *Plasmodium cathemerium* or *Proteosoma praecox*). A number of such inoculated birds are left untreated as controls. The remainder receive daily, for five to six days, a dose of the drug to be tested. In the untreated controls the parasites will appear in the peripheral blood usually after five to seven days. In the birds treated with antimalarial drugs the appearance of the parasites will be retarded. The number of days of retardation is a measure of the efficiency of the drug under trial. By proper modifications of this bird test information can be obtained on whether a substance acts preferably on the asexual or sexual forms. Usually the brief terminology "schizonticidal" and "gametocidal" is used in connection with drugs acting on the asexual and sexual forms respectively.

Before selecting promising antimalarial drugs for clinical trials the so-called chemotherapeutic index has to be established. For this purpose the maximal tolerated dose (T) and the minimal curative dose (C) are determined. The minimal curative dose (C) is the amount of the drug which produces a definite schizonticidal or gametocidal action. The maximal tolerated dose (T) is self-explanatory. The ratio T/C is called the chemotherapeutic index or ratio. A rather large index is only an indication of possible usefulness. Clinical trials have to follow; they will be the decisive factor. In humans, where the general conditions and the species of the parasites differ from birds, the picture may look entirely different.

In discussing the individual modern antimalarials it may be said that according to Webster there are several definitions of "modern", one of them is "characteristic of the present time". The topic of this lecture should be interpreted in this sense. All modern antimalarials have really been known for some time.

It was mentioned at the outset that around the year 1640 cinchona bark was discovered to possess antimalarial properties. Cinchona trees are native on the high eastern slopes of the Andes be-

tween latitudes 10° N. and 20° S. On an average they are found from 5000 to 8000 feet above sea level. Due to the indiscriminate removal of the bark a large number of the cinchona trees were destroyed. Because of this situation a high price of quinine resulted during the middle of the 19th century. This gave an impetus to planting the trees in other parts of the world. All of us know too well that about 90 per cent. of the world's supply of cinchona bark now comes from Java, where especially the species *Cinchona ledgeriana* (or *Cinchona ledgeriana* grafted on *Cinchona succirubra*) is grown. This species furnishes the highest percentage of quinine. The total alkaloid content is about 6 per cent., and the quinine content of these total alkaloids is 70 per cent.

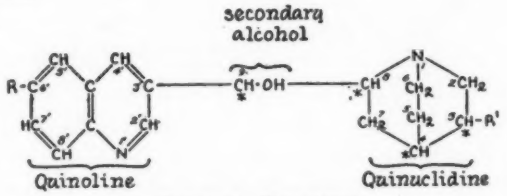
There is also some cultivating of cinchona trees in India and Ceylon, but this has recently decreased because the species *Cinchona succirubra* which is grown there yields 6 per cent. of total alkaloids of which only 30 per cent. is quinine.

It is not generally known that a plantation of more than 1,300,000 cinchona trees has been cultivated in a mountainous region on Mindanao in the Philippines (17). *Cinchona ledgeriana* has been the most promising species as far as yield in alkaloids, particularly quinine, and adaptability to Philippine conditions are concerned. During its last regular session in 1941, the Philippine National Assembly enacted legislation authorizing the establishment, cultivation, maintenance and development of cinchona plantations in public forest lands, and appropriated the necessary funds. It may be concluded that the cinchona bark of the Philippines is in its quality equal to that of Java.

Among the numerous alkaloids which occur in cinchona bark four are of practical importance; namely quinine, quinidine, cinchonidine and cinchonine. The alkaloid content of the bark of *Cinchona ledgeriana* is as follows. The figures for *Cinchona ledgeriana* grafted on *Cinchona succirubra* are similar.

Alkaloid	Per Cent.
Quinine	4.4-5.1
Quinidine	0.16-0.2
Cinchonidine	0.4-0.6
Cinchonine	0.3-0.4
Amorphous alkaloids	0.8-1.6

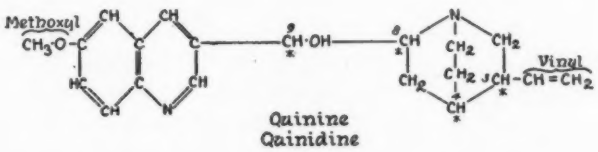
It was not until 1820 that quinine was isolated in a pure form by Pelletier and Caventou. A great number of workers have been engaged in the isolation and the determination of the constitution of the various cinchona alkaloids. Also numerous investigations dealing with the synthetic aspects have been carried out. We owe the final chemical structures of these alkaloids (1908) mainly to the investigations of Rabe, who once taught chemistry at the University of Hamburg. The general structure of these substances may be expressed by the following formula which fundamentally consists of two moieties, the bicyclic quinoline and quinuclidine nuclei which are held together by a single carbon atom which carries a secondary hydroxyl group.



General Structure

R and R′ represent certain radicals which will be discussed later. The carbon atoms marked with asterisks, namely 3, 4, 8 and 9 are so-called asymmetric carbon atoms. This means that, from a theoretical point of view, at each of these carbon atoms two different stereochemical arrangements are possible. Hence each asymmetric carbon atom may contribute to the total optical rotation in a positive or negative sense.

In quinine R is a methoxyl group and R′ is a vinyl group, hence the structure is the following:

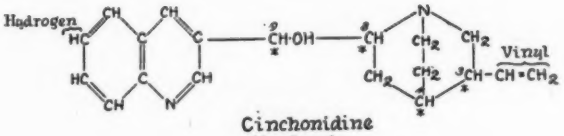


Quinine
Qainidine

Quinidine is a stereoisomer of quinine; therefore, the structural formula is the same. As can be seen from the table these two alkaloids differ only regarding their stereochemical arrangements at carbon atoms 8 and 9.

Alkaloid	$[\alpha]_D$	Direction of rotation C^8	C^4	C^8	C^9	Melting-Point
Quinine	$-158.2°$	+	−	−	−	177°
Quinidine	$+243.5°$	+	−	+	+	168°

In cinchonidine R is a hydrogen atom and R′ is a vinyl group. The structure is as follows:



Cinchonidine
Cinchonine

Cinchonine is a stereoisomer of cinchonidine. As the table shows, the difference consists of the opposite stereochemical arrangements at carbon atoms 8 and 9. Hence the difference is completely analogous to that in the quinine-quinidine series.

	$[\alpha]_D$	Direction of rotation C^8	C^4	C^8	C^9	Melting-Point
Cinchonidine	$-111°$	+	−	−	−	202°
Cinchonine	$+224.4°$	+	−	+	+	260°

Whereas no synthesis of the four discussed alkaloids has been achieved, certain dihydro derivatives have been synthesized by Rabe and his collaborators. In the dihydro derivatives the vinyl side chain appears hydrogenated to an ethyl group. Although these total syntheses are great achievements, they are of no practical consequence.

To the chemist the cinchona alkaloids are of a special interest. Their structure can be changed in numerous ways, and the influence of these modifications on their pharmacological action can be readily tested biologically. They have not only been examined for antimalarial action, but also for their local anesthetic and bactericidal effect. As local anesthetics they have never gained importance. Certain derivatives have served as bactericidal agents, such as Optochin, Eucu-

pine and Vuzine. They are completely replaced by the modern sulfa drugs. Hence Optochin, official in U. S. P. XI, does not appear in U. S. P. XII (but in N. F. VII).

Recently the main cinchona alkaloids were tested according to Roehl's bird malaria method (10). When compared with quinine as the unit the activity of the compounds is as follows:

Dihydroquinine	1-2	Quinidine	about 0.5
Quinine	1	Cinchonine	< 0.2
Dihydroquinidine	0.5-1	Dihydrocinchonine	< 0.2
Cinchonidine	about 0.5	Dihydrocinchonidine	< 0.2

It appears that in bird malaria each levorotatory alkaloid probably affords better protection than its dextrorotatory stereoisomer. The presence of the methoxyl group seems to increase the activity.

In humans, the toxicity of the cinchona alkaloids is comparatively small. Quinine for instance, is rather quickly eliminated from the body. About one-third appears in the urine, a minor part is found in the feces, and the major part seems to be destroyed in the liver. Overdosage leads to symptoms known as cinchonism. By cinchonism is meant a well known complex, characterized chiefly by headache, ringing in the ears and disturbances of vision. A small number of individuals are even sensitive to small doses of quinine. The symptoms of this idiosyncrasy are different from those of cinchonism. Such individuals are sometimes only sensitive to levorotatory cinchona alkaloids. In such cases the dextrorotatory quinidine can be substituted for quinine.

Malaria is the main clinical indication for the use of cinchona alkaloids. Some of these substances, especially quinidine, are also useful for the control of certain types of cardiac arrythmias and tachycardia. Because of their analgetic effect they are also widely used as headache remedies. In this respect they can be replaced by other and better acting agents. The use of quinine in hair tonics is entirely irrational and has caused severe skin reactions in hypersensitive individuals.

Proper treatment with cinchona preparations is usually the method of choice in cases of malaria. Fundamentally, it may be said that in adequate doses quinine destroys, in the peripheral blood, the asexual forms and gametocytes of *Plasmodium vivax* and *Plasmodium*

malariae. In cases of malignant tertian malaria, caused by *Plasmodium falciparum,* only the asexual parasites are eliminated, whereas the gametocytes remain unimpaired. Hence such individuals remain infectious for mosquitoes. It is clearly indicated that cases of malaria are treated as early as possible. In older cases it happens not infrequently that after the treatment with quinine the parasites disappear from the peripheral blood and the patients become free from symptoms. But due to the fact that a large number of parasites have become localized in the capillaries of certain organs, where they cannot easily be reached, relapses are rather frequent.

Proper treatment with so-called prophylactic doses (about 0.65 Gm. daily) of quinine does not produce real chemoprophylaxis in healthy individuals. The sporozoites which enter the blood stream by way of mosquito bites are not destroyed. However, in individuals treated with quinine they will develop rather slowly and the subsequent multiplication of the asexual parasites will be greatly retarded. Hence no clinical symptoms will develop in such individuals so long as they remain under treatment with quinine. Once quinine is withdrawn, attacks of malaria may follow. It is recommended that treatment with quinine be continued for a period of 8 weeks after departure of the individual from the infested area (7).

It appears reasonable, therefore, to protect people living in badly infested areas, and especially soldiers during mobile warfare, by giving them daily prophylactic doses of quinine. During the first world war the number of malaria cases among the allied troops was rather high due to insufficient chemoprophylactic measures. In the East African War of 1916, for instance, there were almost 16,000 admissions (263 deaths) out of only 50,000 allied troops; in other words, one-third became victims of malaria. In contrast with this are the figures given for the Italian army during the Ethiopian campaign (1935-1936). The troops were continuously on the move with their area of operations tremendously extended in very malarious regions. Every soldier took quinine bisulfate tablets, 0.2 Gm. three times daily. Since previous experience had shown that troops were prone to neglect their medication, frequent inspections were made at which time random samplings of urine were taken and tested for quinine with Tanret's reagent. As a result of the routine only 1,214 hospital admissions for primary malaria and 1,093 for relapses (23 deaths) occurred out of an army of 500,000. In other words, less than one per cent. fell victims to the disease (14).

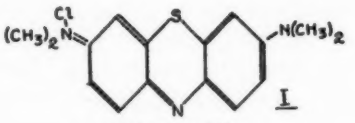
The world production of quinine averages between 600 and 700 tons of quinine sulfate annually (11). The annual consumption within the United States is about 100 tons (18). Increased amounts of antimalarials will be required by the United States due to the needs of the armed forces who are fighting in various malarious regions. With Java in Japanese hands the situation is critical. Increased imports of cinchona bark from South American States may be expected, but will not substantially alter the situation. Due to this emergency the use of cinchona alkaloids in this country is at present restricted to cases of malaria, and that of quinidine, in addition, to certain specific cases of cardiac disorders.

Due to the fact that not only quinine but also the other principal alkaloids of cinchona bark produce antimalarial action the British Pharmacopœia in 1933 introduced Totaquine which contains not less than 70 per cent. of crystallizable cinchona alkaloids. The quinine content of this mixture must be no less than 14 per cent. These requirements permit the utilization of cinchona bark of rather low quinine content. Totaquine was specifically recommended by the Malaria Commission of the Health Organization of the League of Nations. The U. S. P. XII also lists Totaquine. The U. S. P. requirements are: Not less than 10 per cent. of anhydrous quinine, not less than 25 per cent. of cinchonidine and anhydrous quinine combined, and a total of not less than 70 per cent. of cinchonidine, cinchonine, anhydrous quinidine, and quinine. These U. S. P. requirements will be suspended at least for the duration of the war. A new standard will permit the fuller use of South American bark (21). There must be no less than 7 per cent. and no more than 12 per cent. of anhydrous quinine and the total anhydrous crystallizable alkaloids must be no less than 70 per cent. and no more than 80 per cent.

We turn now to the synthetic antimalarials. Numerous investigators have tried to subject the molecule of quinine to various chemical changes with the hope of improving the antimalarial properties of this alkaloid. In the chemical changes were involved mainly the methoxyl, the secondary alcohol and the vinyl groups. As was pointed out, a few bactericidal agents were obtained this way. However, no therapeutically interesting antimalarials resulted from these investigations. Also the introduction of basic groups into the quinine molecule did not produce any increase or modification of antimalarial activity.

In 1891 Paul Ehrlich had found in his investigations on dyes that methylene blue is a very suitable agent for the staining of the Plasmodia of malaria. Hoping that an interrelationship might exist between the parasite and the dye, Ehrlich in cooperation with Guttmann examined methylene blue in cases of human malaria. Even though in the blood of patients apparently no staining of the malaria parasites takes place, there is obviously some chemotherapeutic action, especially in cases of quartan malaria. A number of investigators in the Elberfeld Laboratories of the I. G. Farbenindustrie decided to modify the chemical structure of methylene blue, hoping to improve the plasmodicidal action of this dye (12e). The earlier experiments were concerned with substituting longer alkyl radicals for the methyl groups of the aromatic amino groups. When tested in cases of bird malaria these compounds (for instance II and III) proved to be somewhat more effective than methylene blue. The chemotherapeutic indices, on the other hand, showed no improvement.

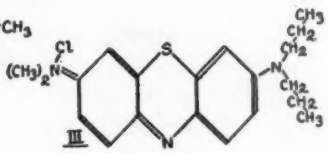
It was then decided to introduce basic alkyl groups into the aromatic amino groups of methylene blue. Although compound IV showed only a slight increase of plasmodicidal activity, the chemotherapeutic index appeared definitely improved. On the other hand, compound V which contains a somewhat longer and branched basic alkyl group manifested a considerably increased plasmodicidal action. In addition, the chemotherapeutic index was 8, whereas that of compound IV was only 2.



I

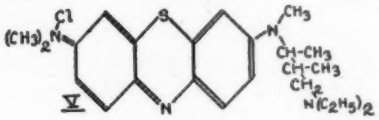
Methylene Blue

II



III

IV



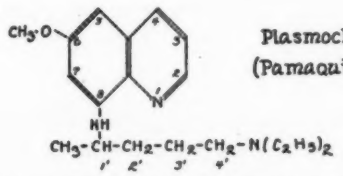
V

The studies on the molecule of methylene blue in which were included the examples above mentioned and many others led to the conclusion that the introduction of basic alkyl groups in the aromatic amino group brings about an increase of plasmodicidal action. Furthermore, it was concluded that certain interrelationships exist between the degree of action and the length as well as the structure (branching) of the basic alkyl groups.

The results thus obtained were a stimulus to introduce similar groups into various other ring systems. A very large number of chemical compounds was prepared and subjected to pharmacological tests. A certain number of these substances was subsequently selected for clinical trials. The result of these investigations really represents one of the greatest triumphs of systematic chemotherapeutic research.

The work in the Elberfeld Laboratories was carried out under the scientific director Heinrich Hörlein. As can be anticipated, the credit belongs to a large number of investigators. Two preparations have become widely known. Plasmochin was synthesized in 1924 (21h) by Schulemann, Schönhöfer, and Wingler; it was pharmacologically tested by Roehl. Atabrine was synthesized in 1930 (21h) by Mietzsch and Mauss. Because Roehl had died, the pharmacological examination was carried out by his successor Kikuth. Both preparations were first tested clinically by Mühlens and his colleagues in the Institute and Hospital for Tropical Diseases in Hamburg. Since then these chemotherapeutic agents have been used clinically in numerous tropical and subtropical regions of the whole world.

Plasmochin is a quinoline derivative. In that respect and also regarding the position of the methoxyl group it resembles quinine, although otherwise its structure is different.



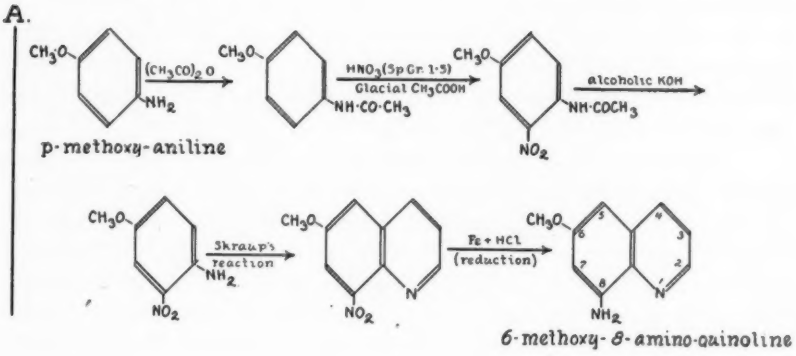
Plasmochin
(Pamaquine USP XII)

6-methoxy-8-(1'-methyl-4'-diethylamino)butylamino-quinoline

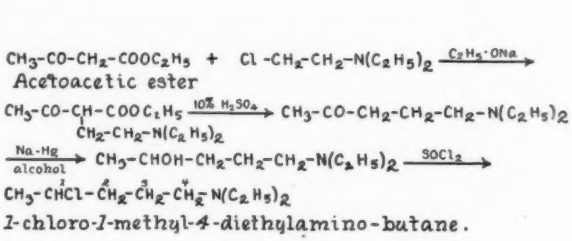
As can be seen, the chemical structure is comparatively simple. The synthesis appears conceivable according to the following scheme (8)

although it appears doubtful whether the technical process actually follows this line.

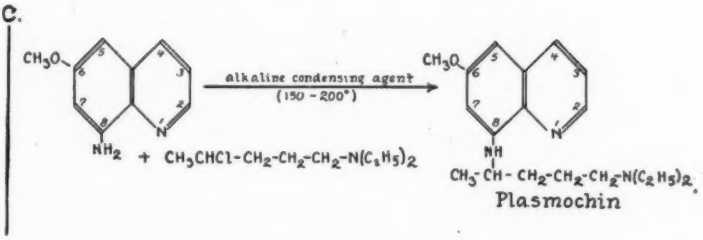
A.



B.



C.



Plasmochin is one of the most specific and potent antimalarials. The chemotherapeutic index, as determined by Roehl in canaries, is 30 whereas, under analogous conditions, that of quinine is only 4. The effect on the asexual forms (schizonts) of the malaria parasites is only slight. In this respect it definitely does not compare favorably with quinine. It possesses, however, a selective and very powerful action on the gametocytes of all species of Plasmodium. It is there-

fore clearly different from quinine which does not act upon the sexual forms of the parasites causing the tropical form of malaria. Hence plasmochin will make any case of human malaria non-infectious for mosquitoes. It will interrupt the vicious cycle of the malaria parasites: man-mosquito-man. Therefore, the systematic administration of plasmochin to carriers of any type of malaria should aid greatly in the eradication of this disease. This, of course, would be very important from the public health standpoint.

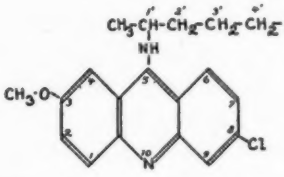
Plasmochin appears to be almost completely destroyed in the body, only traces can be found in the urine. The toxicity varies considerably with the species of animals, not only quantitatively but also qualitatively. It was mentioned that in birds the margin of safety is greater than that of quinine. In humans, however, the margin of safety is rather narrow. The administration of plasmochin is safe only under constant medical supervision. Unlike in quinine prophylaxis, it seems generally agreed that the administration of plasmochin must be restricted to patients who can be seen regularly by a physician. This, of course, presents a serious obstacle to its wholesale use in the control of malaria.

Because of its toxic properties plasmochin cannot be safely given in doses large enough to eliminate the schizonts as well as the gametocytes. Since relatively small doses are sufficient to destroy the gametocytes, it is recommended that small amounts of plasmochin be combined with quinine. This combination destroys schizonts and gametocytes alike; in addition, it lessens the rate of relapses. Such combined preparations are on the market under the names "Plasmochin Compound" or "Chinoplasmin".

It should be added that plasmochin does not act on the sporozoites which are transmitted by the mosquitoes. Hence, like quinine, it is no true chemoprophylactic agent. Plasmochin naphthoate is listed as Pamaquine Naphthoate in the U. S. P. XII. It has not been accepted for inclusion in the N. N. R. Plasmochin preparations are manufactured in this country by the Winthrop Chemical Company.[8]

[8] Other preparations identical with plasmochin are Praequine, Fourneau 710, Rhodoquine and Plasmocide. Preparations similar to plasmochin regarding structure and action are Fourneau 915 or Rodoquine V and Certuna (I. G. Farbenindustrie. Originally called "Cilional"). The latter substance is 6-hydroxy-8 (4'-dimethylamino-butyl-2'-amino) quinoline combined with methylenebis-2-hydroxynaphthoic acid. It may be concluded from the few available reports that the action appears to be closely allied to that of plasmochin and that it is possibly less toxic. It does not act upon the sporozoites, hence it cannot be considered a true chemoprophylactic (1, page 107) (6).

The second important synthetic antimalarial is atabrine. It represents a derivative of acridine which, in part, contains the quinoline ring system. The derivatives of acridine are yellow dyes. To this type of compounds also belongs Acriflavine (Trypaflavine) which was in vogue for its bactericidal properties. In atabrine the methoxyl group is in a position analogous to that in the molecule of plasmochin. The side chain is identical with that of the plasmochin structure, although it is attached in a non-analogous position.



Atabrine[4]
(Quinacrine U.S.P. XII)

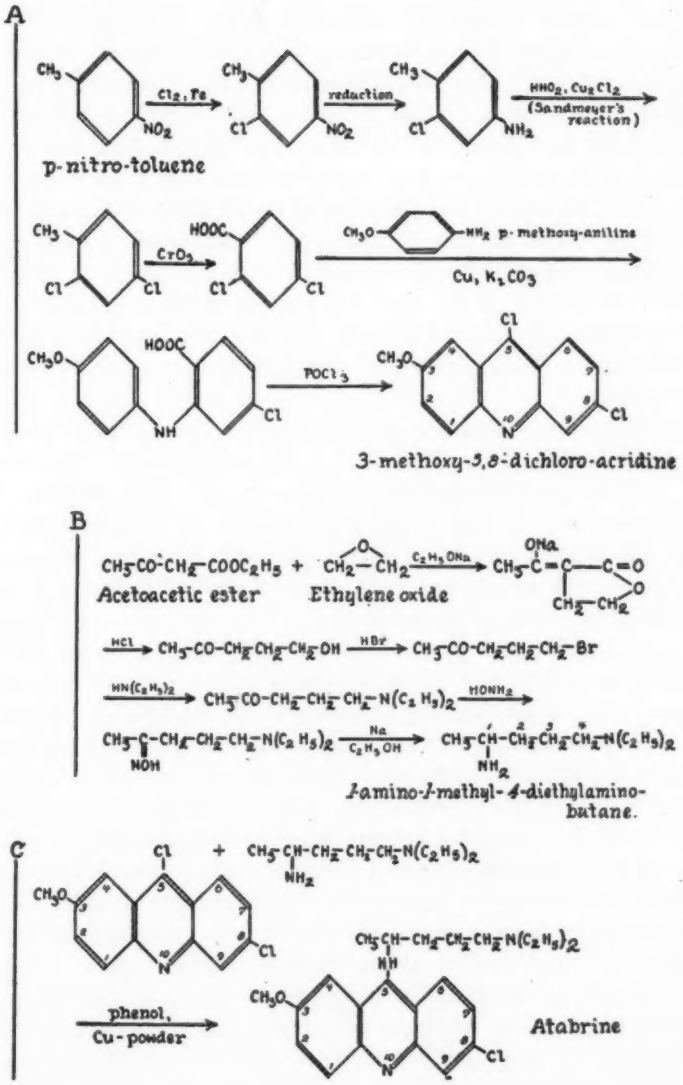
3-methoxy-5-(1'-methyl-4'-diethylamino)butylamino-8-chloro-acridine.

The synthesis of atabrine appears conceivable according to the scheme on the opposite page (8). The technical process probably contains various modifications, especially as far as the preparation of the side chain is concerned.

It may be added that the presence of a substituent at carbon atom 8 is essential for a strong schizonticidal action. Also a compound substituted by a methyl group rather than a chlorine atom is an efficient schizonticidal agent (12i, page 355).

As was mentioned, plasmochin acts preferably upon the gametocytes of the malaria parasites. Atabrine, on the other hand, exercises a definite action upon the schizonts of all known species of malaria, whereas there is no comparable action upon the gametocytes. Thus it is curative in the same sense as quinine. The potency of atabrine as compared with quinine in human malaria has been the subject of considerable study. There is little evidence that it is superior to the cinchona alkaloids.

[4] The numbering of the atoms is according to the older custom of Chemical Abstracts. The alternative numbering which follows the more recent convention (1937) is given in parentheses: 1 (5), 2 (6), 3 (7), 4 (8), 5 (9), 6 (1), 7 (2), 8 (3), 9 (4), 10 (10). Hence, according to the newer nomenclature, used in N. N. R., atabrine is 3-chloro-7-methoxy-9-(1'-methyl-4'-diethylamino) butylamino-acridine. Because the molecule of acridine is symmetrical, the newer nomenclature also permits for atabrine the designation 6-chloro-9-(4'-diethylamino-1'-methyl-butylamino)-2-methoxy-acridine (e. g. Chem. Abstr. from 1938 on).



The chemotherapeutic index of atabrine is 30. As with plasmochin, the toxicity varies considerably with the species of animals. Even though the margin of safety in humans is large, it is very slowly eliminated; hence the danger of a cumulative effect exists. A

certain amount is excreted unchanged in the feces and in the urine; the figures given in the literature vary considerably. Atabrine has been found in the urine of patients as late as 9 weeks after the termination of treatment. It has therefore been suggested that treatment should not be repeated within an interval of less than 8 weeks. The total amount during any period of treatment should not exceed 2 Gm. (0.3 Gm. per day). For purposes of prophylaxis 0.2 Gm. of atabrine may be given on two consecutive days of each week or even at longer intervals. Since atabrine is a yellow dye, it is liable to give rise to yellow coloration of the skin, but this is in no way harmful and is not regarded as a toxic symptom. Besides, it is a temporary manifestation which disappears within about two weeks after cessation of treatment.

Whereas quinine can be safely given jointly with plasmochin (chinoplasmin) it is claimed that the simultaneous administration of atabrine and plasmochin produces rather toxic effects. If the administration of both drugs is desired, it is recommended not to give plasmochin before the conclusion of the treatment with atabrine. It is said that such a treatment causes a marked decrease in relapses in the three forms of malaria.

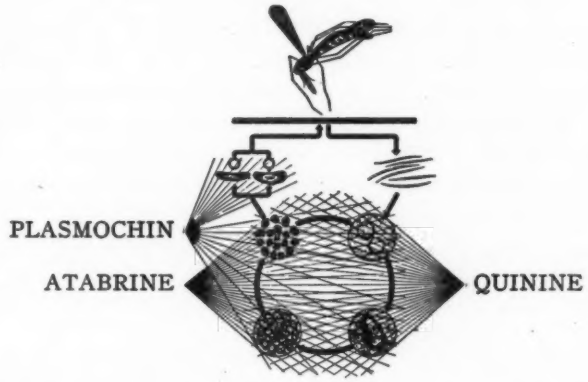
As quinine and plasmochin, atabrine does not act on the sporozoites, hence it is no true chemoprophylactic agent. It does not prevent infection but will only retard the development of the parasites.

In general atabrine can be considered to be a very efficient substitute for quinine. The dihydrochloride of atabrine is included in the U. S. P. XII as Quinacrine Hydrochloride.[5] It is also listed in the N. N. R. Atabrine preparations are manufactured in this country by the Winthrop Chemical Company, and to some extent, also by Merck and Company. Due to the critical quinine situation there is a great demand for atabrine. The production is now rapidly approaching a rate of 600 million tablets (60 tons) a year (19).[5a] Due to improvements in the manufacturing process the price has been gradually reduced. The manufacturer claims that the cost of medication is now 6¾ cents per case, as compared with 27 cents for quinine (19).

[5] Other synonyms are Atebrin (I. G. Farbenindustrie), Mepacrine (Brit. Pharmacop.), and Acriquine (6).

[5a] In a broadcast over the Red Network, on December 20, 1942, it was announced by Dr. Morris Fishbein, secretary of the Amer. Med. Assoc., and Dr. Theodore G. Klumpp, president of the Winthrop Chemical Company, that the annual production has risen to almost one billion tablets.

In summarizing, it may be said that all modern antimalarials are, in a sense, quinoline derivatives. It is not known whether these agents attack the parasites directly or, what is more likely, whether they stimulate the leucocytes to cope with the parasites more efficiently. The effects of quinine, atabrine and plasmochin are clearly expressed by the following diagram:[6]



It can easily be recognized that all forms of the parasites except the sporozoites can be brought under control.

Since the discovery of plasmochin and atabrine an exceedingly large number of compounds with similar constitution have been synthesized in various parts of the world. In spite of manifold modifications of the structures no compound has been obtained which has proved superior to these two agents. Also numerous compounds of completely different chemical types have been examined for antimalarial action. The only group in which certain encouraging results have been obtained are the so-called sulfa drugs. As was emphasized before, an antimalarial with true chemoprophylactic action (i. e. acting on the sporozoites) still has to be found.

A compilation in table form of all compounds which were either examined for antimalarial action or which otherwise appear interesting was published by Shriner and Upson in 1941 (8). This review, compiled for private[7] circulation, also contains some compounds with trypanocidal action. A confidential[7] compilation "Antimalarials:

[6] The diagram was reproduced from an article by W. Schulemann (12-h, page 325).

[7] The author is greatly indebted to Dr. R. L. Shriner and to Parke, Davis and Company, for permission to cite their respective reviews.

Natural and Synthetic", including the literature up to August, 1942, was very recently (October, 1942) published by Parke, Davis and Company in cooperation with Harry S. Mosher of Pennsylvania State College (8a). This report is more complete than the one mentioned before. The National Research Council has been given the privilege of circulating it.

In this country extensive investigations are being performed in various commercial and non-commercial laboratories. Since 1938 the National Institute of Health in Bethesda, Maryland, has likewise been contributing to this effort. To the numerous agencies concerned with these tasks belongs also the National Research Council, which, besides other activities in this field, organizes the information on the preparation and testing of antimalarial drugs for the convenience of those working on this subject.

Addendum: In the meanwhile a brief outline has been published (22) which covers the present legal restrictions regarding the use of antimalarials. A scheme of dosage is included.

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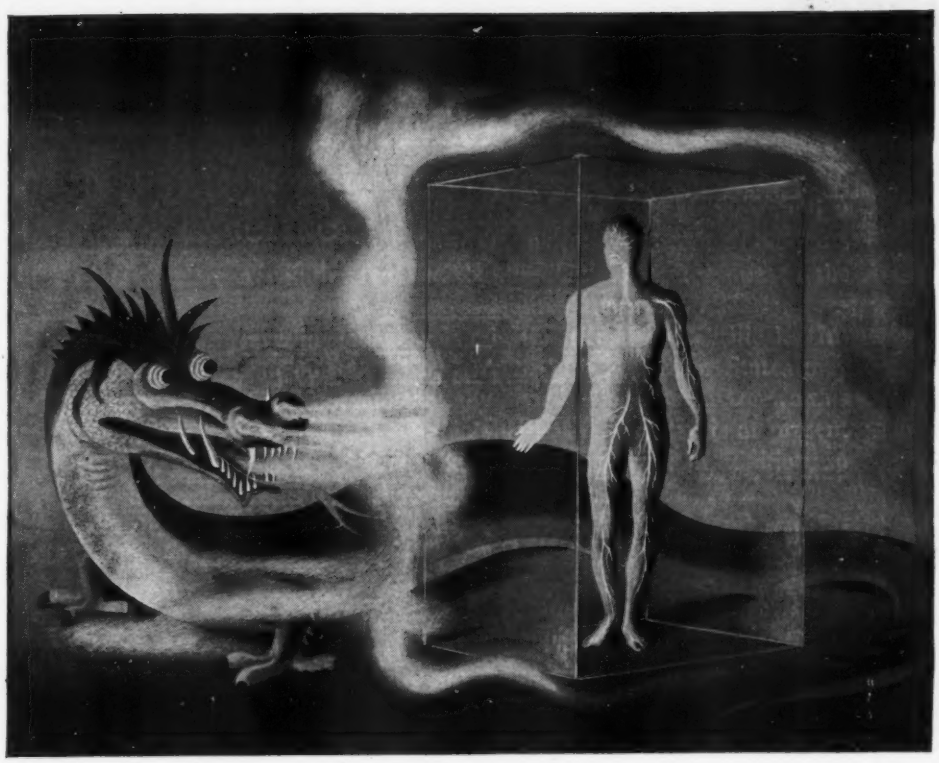

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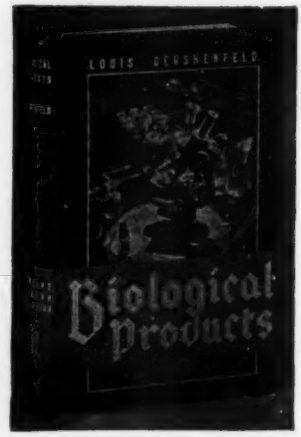

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